IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICANT	: Jackowski *et al.*
INVENTION	:**Plasma Protease C1 Inhibitor Biopolymer Markers Indicative Of Alzheimers Disease**
SERIAL NUMBER	: 09/991,799
FILING DATE	: November 23, 2001
EXAMINER	: Chernyshev, Olga N.
GROUP ART UNIT	: 1646
OUR FILE NO.	: 2132.086

CERTIFICATE UNDER 37 CFR 1.8(a)
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DECLARATION UNDER 37 CFR § 1.132

I, Ferris H. Lander, do hereby declare as follows:

1. I am a registered Patent Agent and am authorized to represent the inventor's and assignee in the application entitled **"Plasma Protease C1 Inhibitor Biopolymer Markers Indicative Of Alzheimers Disease "**, having U.S. Application Serial No. 09/991,799 filed November 23, 2001.

2. In the Office Action mailed on May 19, 2003, claims 1 and 2 were rejected under 35 U.S.C. 112, first paragraph because the claimed invention allegedly contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims as amended have been limited to a specific biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 (the 1826 dalton marker)useful in methods and kits for diagnosing Alzheimers disease. The method of the invention as recited in claim 39 involves a comparison of the mass spectrum profile of a peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 to mass spectrum profiles of peptides elucidated from a patient sample, wherein recognition of a mass spectrum profile in the patient sample displaying the characteristic profile of the mass spectrum of the peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 indicates that the patient from which the sample was obtained is suffering from Alzheimers disease.

3. In order to provide data which would further support the ability of the claimed peptide to function as a diagnostic for Alzheimers disease, I contacted Dr. George Jackowski, Chairman and Chief Science Officer of Syn-x Pharma Inc., and asked to be provided with evidence of the absence of the 1826 dalton marker in normal human sera (obtained from healthy patients).

4. This declaration (including the attached figure) is provided in order to show a comparison of the serum profile of individuals having Alzheimers disease to the serum profile of non-diseased individuals, so as to evidence that the marker (the 1826 dalton peptide) was not present in normal human sera.

The attached figure, obtained from Dr. Jackowski from data derived from the original experiments carried out at the time of conception of the instant invention, provides side-by-side profiles (obtained using techniques of mass spectrometry) of normal human sera versus sera from patients having Alzheimers disease. This profile comparison clearly evidences the absence of the 1826 dalton marker in normal human sera.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

8/18/2003
Date

Ferris H. Lander
Reg. No. 43,377

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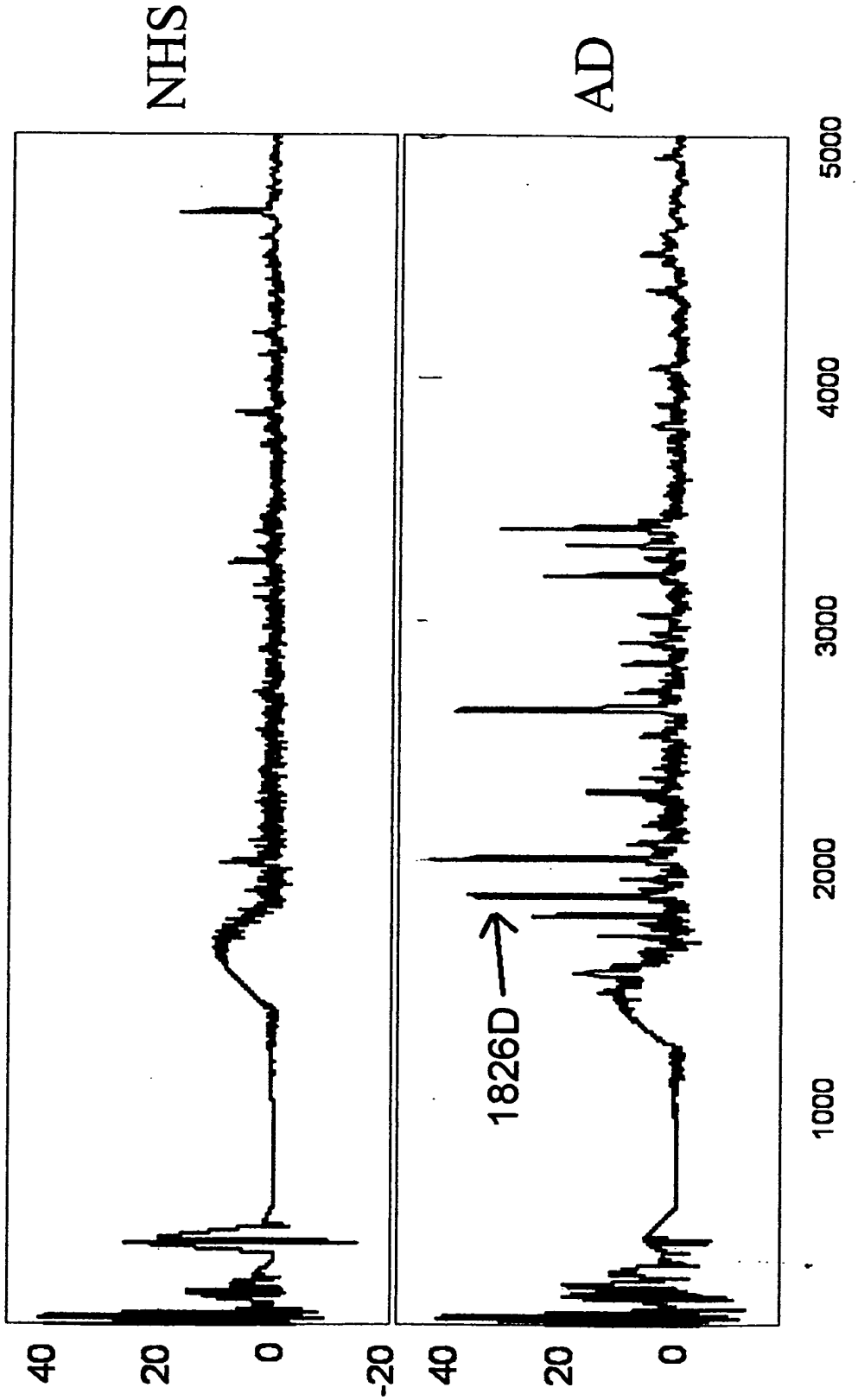

1: Proc Natl Acad Sci U S A. 1992 Dec 15;89(24):11949-53.

Detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer diseased patients: a potential diagnostic biochemical marker.

Gunnersen D, **Haley B**.

Department of Biochemistry, College of Pharmacy, University of Kentucky, Lexington 40536-0084.

In this report, 8- and 2-azidoadenosine 5'-[gamma-32P]triphosphate were used to examine cerebrospinal fluid (CSF) samples for the presence of an ATP binding protein unique to individuals with Alzheimer disease (AD). A 42-kDa ATP binding protein was found in the CSF of AD patients that is not observed in CSF from normal patients or other neurological controls. The photolabeling is saturated with 30 microM 2-azidoadenosine 5'-[gamma-32P] triphosphate. Photoinsertion can be totally prevented by the addition of 25 microM ATP. Photoinsertion of 2-azidoadenosine 5'-triphosphate into the protein is only weakly protected by other nucleotides such as ADP and GTP, indicating that this is a specific ATP binding protein. A total of 83 CSF samples were examined in a blind manner. The 42-kDa protein was detected in 38 of 39 AD CSF samples and in only 1 of 44 control samples. This protein was identified as glutamine synthetase [GS; glutamate-ammonia ligase; L-glutamate:ammonia ligase (ADP-forming), EC 6.3.1.2] based on similar nucleotide binding properties, comigration on two-dimensional gels, reaction with a polyclonal anti-GS antibody, and the presence of significant GS enzyme activity in AD CSF. In brain, GS plays a key role in elimination of free ammonia and also converts the neurotransmitter and excitotoxic amino acid glutamate to glutamine, which is not neurotoxic. The involvement of GS, if any, in the onset of AD is unknown. However, the presence of GS in the CSF of terminal AD patients suggests that this enzyme may be a useful diagnostic marker and that further study is warranted to determine any possible role for glutamate metabolism in the pathology of AD.

PMID: 1361232 [PubMed - indexed for MEDLINE]

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C1 INH
C1 inhibitor, a regulatory molecule that inhibits complement C1 activity.

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1: Brain Res. 1995 Mar 27;675(1-2):75-82.

Complement C1 inhibitor is produced by brain tissue and is cleaved in Alzheimer disease.

Walker DG, Yasuhara O, Patston PA, McGeer EG, McGeer PL.

Kinsmen Laboratory of Neurological Research, University of British Columbia, Vancouver, Canada.

C1 inhibitor was identified in human brain tissue by Western blotting and by immunohistochemistry using multiple antibodies to the native protein. The presence of C1 inhibitor mRNA was identified by reverse transcriptase-polymerase chain reaction analysis of brain mRNA extracts. The mRNA was also detected in cultured postmortem human microglia and in the IMR-32 human neuroblastoma cell line. Immunohistochemically, the native protein was detected in residual serum of capillaries and pyramidal neurons of both control and Alzheimer disease cases, as well as in occasional senile plaques of Alzheimer tissue. The reacted protein was detected on dystrophic neurites and neuropil threads in Alzheimer tissue by 4C3 monoclonal antibody, which recognizes a neoepitope following suicide inhibition. These data indicate that C1 inhibitor, a regulatory molecule controlling multiple inflammatory proteolytic cascades, is produced in normal brain. In Alzheimer disease, C1 inhibitor undergoes a prominent reaction in abnormal neuronal processes, such as dystrophic neurites and neuropil threads.

PMID: 7796155 [PubMed - indexed for MEDLINE]

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Detection of the membrane inhibitor of reactive lysis (CD59) in diseased neurons of Alzheimer br[Brain Res. 1991]

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1: Am J Pathol. 1999 Mar;154(3):927-36.

Up-regulated production and activation of the complement system in Alzheimer's disease brain.

Yasojima K, Schwab C, McGeer EG, McGeer PL.

Kinsmen Laboratory of Neurological Research, University of British Columbia, Vancouver, British Columbia, Canada.

We used reverse transcriptase-polymerase chain reaction and Western blotting techniques to measure the levels of complement mRNAs and their protein products in Alzheimer's disease (AD) brain compared with non-AD brain. mRNAs for C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, and C9 were detected in the 11 regions of brain that were investigated. The mRNA levels were markedly up-regulated in affected areas of AD brain. In the entorhinal cortex, hippocampus, and midtemporal gyrus, which had dense accumulations of plaques and tangles, C1q mRNA was increased 11- to 80-fold over control levels, and C9 mRNA 10- to 27-fold. These levels were substantially higher than in the livers of the same cases. Western blot analysis of AD hippocampus established the presence of all of the native complement proteins as well as their activation products C4d, C3d, and the membrane attack complex. These data indicate that high levels of complement are being produced in affected areas of AD brain, that full activation of the classical complement pathway is continuously taking place, and that this activation may be contributing significantly to AD pathology.

PMID: 10079271 [PubMed - indexed for MEDLINE]

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